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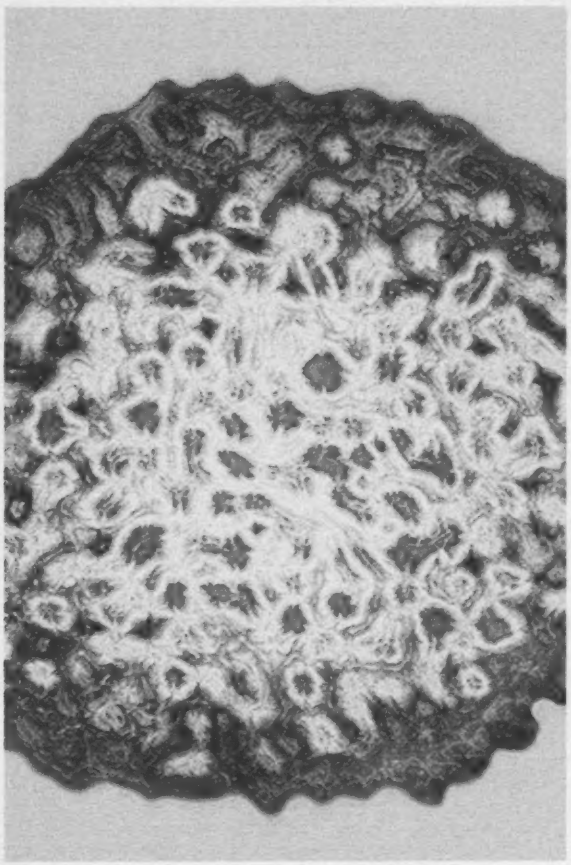
CANADA COMMUNICABLE DISEASE REPORT

INFECTIOUS DISEASE AS CHRONIC DISEASE



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CANADA COMMUNICABLE DISEASE REPORT

The Canada Communicable Disease Report (CCDR) is a bilingual, peer-reviewed, open-access, online scientific journal published by the Public Health Agency of Canada (PHAC). It provides timely, authoritative and practical information on infectious diseases to clinicians, public-health professionals, and policy-makers to inform policy, program development and practice.

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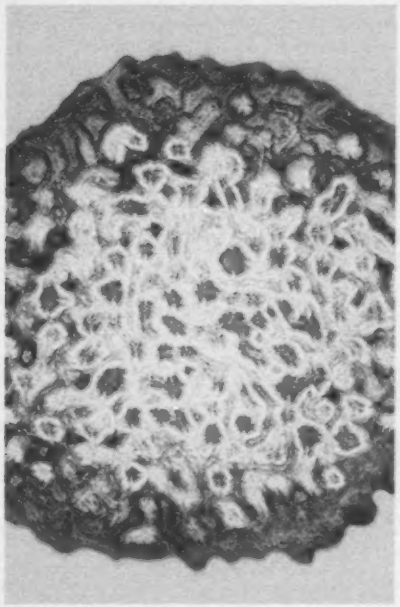

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Comparing the care needs of people living with and without HIV in Canadian home and long-term care settings

Foebel AD[1*], Hirdes JP[1], Boodram C[2], Lemick R[3], Tai JW[3], Comeau RL[2]

Abstract

Background: With the advent of highly active antiretroviral therapy (HAART), HIV has become a manageable chronic infection and individuals with it are living longer. Older individuals with HIV will begin to seek services across the continuum of health care. Whether their care needs differ from those who are HIV negative has not been well-characterized.

Objectives: To compare the demographic characteristics, chronic conditions, presence of infections, and mental health issues among HIV-positive versus HIV-negative individuals in home care, long-term care and complex continuing care settings across Canada.

Methods: This cross-sectional study used interRAI data to compare characteristics of HIV-positive and HIV-negative individuals in long-term care, complex continuing care and home care settings. Chi-square analyses explored differences between groups on co-infections, chronic disease and mental health issues.

Results: Data from 1,200,073 people were analyzed of whom 1,608 (0.13%) had HIV. Overall, HIV-positive individuals had more co-infections but fewer chronic diseases than their HIV-negative counterparts. Depression, social isolation and the use of psychotropic medications were generally more prevalent in the HIV-positive cohort.

Conclusion: People living with HIV make up a small cohort of people with complex needs in home care and institutional settings and their care needs differ from those who are HIV negative. As HIV-positive people age, a better understanding of the context in which these issues are experienced will support appropriate interventions.

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Introduction

In many developed countries, advances in HIV management, namely highly active antiretroviral therapy (HAART), mean that HIV infection has become a chronic disease. For persons living with HIV-AIDS (PHAs), comorbidity profiles are shifting away from AIDS-defining illnesses toward HIV-associated non-AIDS illnesses such as cardiovascular and kidney diseases (1,2). Further, approximately two-thirds of older PHAs now live with other chronic conditions (3-11). The onset of these chronic conditions occurs earlier than in HIV-negative individuals (1,5,11) and comorbidity includes more infections due to immune suppression and HAART (1,2,12). Finally, despite advances in HAART, HIV-associated neurocognitive disorders are well-described long-term outcomes of HIV infection (13). This population likely differs greatly from younger PHAs and older adults without HIV, making the particular care needs of older PHAs unique.

HIV prevalence in Canada is expected to follow US projections, where it is estimated that half of HIV-positive individuals will be 50 years or older by 2050 (14). This demographic shift will have important implications for disease management and the choice of care setting for these individuals. It is likely that many adults with HIV will eventually seek support, treatment and care services in non-acute settings such as the home and long-term care (15). Whether these service providers are prepared to meet the unique care needs of these individuals is not known, but as individuals with HIV increasingly seek care options, pressure on such systems to respond will also increase.

interRAI standardized assessment data can help to establish whether care needs are being met across multiple health care settings in Canada. interRAI is an international not-for-profit research consortium initially established by clinicians and researchers with the goal of improving the quality of care and the quality of life in nursing homes in the USA (www.interRAI.org) (16,17). The interRAI assessment instruments

were designed to provide a common, integrated approach to standardized assessment of vulnerable populations with complex care needs, such as those requiring home care and nursing home services (16,18-20). The minimum data set version 2.0 (MDS 2.0) and interRAI Home Care (RAI-HC) instruments have been validated for use in the home care and long-term care settings, respectively (19-21). Although these instruments have been in use in Canada since 1996 and 2002, respectively, they have not been used to track the health care needs of HIV-positive individuals.

Currently, there is little evidence about the needs of HIV-positive individuals in home care or institutional environments. The objective of this study was to compare the care needs of people living with and without HIV in Canadian home care and long-term care settings, with a focus on co-infections, comorbidities and mental health issues.

Methods

Settings

This study included data from Canadian home care (HC), long-term care (LTC) and complex continuing care (CCC) settings, which are defined in the following text box.

Definitions of care settings

Home care (HC): Services that include a mix of personal support, home nursing and some rehabilitative care that are provided in a client's home. Note: Long-stay clients are expected to be using services for 60 days or more.

Long-term care (LTC): Private, public and charitable nursing homes that provide regulated care to people with stable medical conditions who require 24-hour care.

Complex continuing care (CCC): Hospitals or units in post-acute hospital settings that provide care to individuals with more severe impairments or more medically complex conditions and/or mental health needs than those who typically cared for in nursing homes. Note: These facilities are only available in Ontario and Manitoba.

Data from two Canadian interRAI assessment instruments were used to capture information about these three settings. Data for the home care sample were collected using the interRAI Home care (RAI-HC) instrument and data for the institutionalized samples (in LTC and CCC) came from the interRAI minimum data set version 2.0 (MDS 2.0) instrument. Data from these instruments were available from two national repositories managed by the Canadian Institute for Health Information (CIHI), the Home Care Reporting System (HCRS) and the Continuing Care Reporting System (CCRS) (22,23). Data-sharing agreements between CIHI, interRAI and the University of Waterloo allowed access to these data for this research. RAI-HC data were collected from 2002–2014 for all long-stay home care clients. For the LTC and CCC populations, MDS 2.0 assessments were collected between 1996 and 2014.

Population

All individuals in these settings were included in the study provided they had a completed interRAI assessment. RAI-HC assessments from hospital settings were excluded as those assessments determine LTC eligibility and not home care planning.

The home care sample included individuals from British Columbia, Manitoba, Ontario, Nova Scotia and Yukon. The LTC sample included individuals from Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Nova Scotia, Ontario, Saskatchewan and Yukon. CCC data were available from Ontario and Manitoba.

Measures

interRAI instruments contain a comprehensive set of core items to describe client demographics and clinical characteristics that assist with care planning. Demographic information about age, sex and marital status (where "married" indicates married or common-law partners, including same-sex partners) are available from all interRAI records.

The measures included in this study comprised common chronic conditions associated with aging and conditions for which PHAs may be at higher risk (including infections and mental health comorbidities). Most data were available from both the RAI-HC and MDS 2.0 instruments. In both instruments, checklists of disease diagnoses are available for all of the chronic diseases (heart failure, emphysema/chronic obstructive pulmonary disease [COPD], diabetes, cancer, any psychiatric disorder and other cardiovascular diseases) and infectious diseases (pneumonia, tuberculosis and urinary tract infections [UTI]) assessed in this study. However, some infectious diseases (antibiotic-resistant infections, cellulitis, *Clostridium difficile* infection, conjunctivitis, respiratory infections, septicemia, sexually transmitted infections [STIs] and viral hepatitis) were only available from checklist items available on the MDS 2.0 and could not be measured in the home care sample.

For mental health symptoms (including anxiety, aggressive behaviour, hallucinations and social isolation), specific items record the presence or absence of the symptom on both the RAI-HC and the MDS 2.0. Depressive symptoms were examined using the Depression Rating Scale embedded within both interRAI assessment instruments; a score of three or higher on this scale indicated possible depression (24). The instruments also record the use of any psychotropic medications (antipsychotics, antidepressants, anxiolytics and sedatives) in the previous seven days.

Analysis

Differences in characteristics between HIV-positive and HIV-negative individuals in each care setting were tested using chi-square tests (significance level $p < 0.05$) for all variables of interest. Age was collapsed into six categories to differentiate very young as well as very old individuals. All analyses were carried out using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina).

Results

The total sample comprised 1,200,073 people (**Table 1**). HIV prevalence was 0.13%, which is slightly lower than that of the general Canadian population (0.21% in 2014) (25); a large proportion of the sample came from Ontario (76%). The long term care sample included 356,621 people; overall HIV prevalence was 0.05%, but in 5 regions (New Brunswick, Newfoundland and Labrador, Nova Scotia, Saskatchewan and Yukon), there were no recorded HIV cases. The HIV prevalence rate in CCC was much higher at 0.19%. Finally, the large home care sample (n = 618,301) had an overall HIV prevalence rate of 0.16%, ranging from 0.07% in Nova Scotia to 0.49% in British Columbia.

Table 1: Summary of study sample by care setting, Canada (n = 1,200,073)

Care setting	HIV/AIDS	Total	HIV prevalence (%)
Long-term care[1]	178	356,621	0.05
Complex continuing care[2]	423	225,151	0.19
Home care[3]	1007	618,301	0.16
TOTAL	1608	1,200,073	0.13

Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus
[1]Sample from Alberta (10%), British Columbia (17%), Manitoba (4%), New Brunswick (<1%), Newfoundland (<1%), Nova Scotia (<1%), Ontario (58%), Saskatchewan (9%) and Yukon (<1%)
[2]Sample from Manitoba (0.3%) and Ontario (99.7%)
[3]Sample from British Columbia (11%), Manitoba (2%), Nova Scotia (8%), Ontario (78%) and Yukon (<1%)

Table 2 shows the demographic and diagnostic characteristics of the sample. The HIV-positive and HIV-negative groups differed on some key characteristics in the three care settings. Approximately 60%–65% of the people in the HIV-negative groups across the settings were female, compared with 20%–30% of people in the HIV-positive groups. Between 95% and 99% of HIV-negative people were over 50 years of age compared with 47%–72% of HIV-positive people. Marriage rates in the HIV-positive groups were half those of the HIV-negative groups, and men were less likely to be married than women, except in home care where both men and women with HIV were less likely to be married.

Co-infections

Disease diagnoses varied by care setting (**Table 2**). Infectious disease rates varied, but higher rates of pneumonia were seen in the HIV-positive groups in CCC and home care. The HIV-positive

Table 2: Demographic characteristics, co-infections, comorbid disease diagnoses and mental health characteristics of the Canadian sample, by care setting (n = 1,200,073)

Characteristics	Long-term care (%)			Complex continuing care (%)			Home care (%)		
	Non HIV (n = 356,443)	HIV 178	p value	Non HIV 224,728	HIV 423	p value	Non HIV 617,294	HIV 1,007	p value
Age (years)			<0.0001			<0.0001			<0.0001
0–39	0.3	5.6		1.3	20.8		2.2	11.1	
40–49	0.6	18.5		2.3	31.9		3.0	29.6	
50–64	4.2	43.3 =		10.5	28.1		11.6	37.5	
65–74	8.5	18.5		18.0	9.5		14.8	11.3	
75–84	28.0	10.7		36.7	5.7		33.0	6.3	
85+	58.4	NR		31.4	4.0		35.4	4.2	
Female	65.8	22.5	<0.0001	57.6	26.5	<0.0001	62.8	30.3	<0.0001
Married	23.0	10. 7	<0.0001	39.2	18.0	<0.0001	38.1	12.4	<0.0001
Male	39.3	9.4	<0.0001	55.5	17.0	<0.0001	56.5	11.6	<0.0001
Female	14. 5	15.0	0.92	27.2	20.5	0.11	27.6	14.5	<0.0001
Infections									
Pneumonia	2.6	3.9	0.28	7.3	13.2	<0.0001	2.9	9.8	<0.0001
Tuberculosis	0.1	NR	NR	0.1	2.6	<0.0001	0.1	4.1	<0.0001
UTI	7.0	6.7	0.88	16.5	9.5	<0.0001	4.8	6.1	0.05
Antibiotic-resistant	4.0	12.4	<0.0001	6.7	9.9	0.007	n/a	n/a	n/a
Cellulitis	1.0	NR	NR	1.5	3.6	0.0005	n/a	n/a	n/a
Clostridium difficile	0.6	NR	NR	2.0	5.0	<0.0001	n/a	n/a	n/a
Conjunctivitis	0.5	0	0.34	0.6	1.9	0.0003	n/a	n/a	n/a
Respiratory infection	2.7	NR	NR	3.6	4.5	0.3	n/a	n/a	n/a
Septicemia	0.6	NR	NR	1.4	4.5	<0.0001	n/a	n/a	n/a
STIs	0.1	6.7	<0.0001	0.1	12.1	<0.0001	n/a	n/a	n/a
Viral hepatitis	1.2	23.6	<0.0001	0.5	18.7	<0.0001	n/a	n/a	n/a
Diagnosis									
Heart failure	15.4	6.4	0.001	14.1	4.7	<0.0001	13.0	6.1	<0.0001
Emphysema/COPD	17.1	18.6	0.61	18.3	14.7	0.05	17.7	19.8	0.09
Diabetes	24.7	24.2	0.87	25.5	12.4	<0.0001	25.2	15.6	<0.0001
Cancer	10.9	8.1	0.25	27.5	17.5	<0.0001	17.7	12.5	<0.0001
Any psychiatric	53.4	52.8	0.87	40.6	48.0	0.002	30.0	46.2	<0.0001
Other CVD	66.1	32. 6	<0.0001	60.4	27.2	<0.0001	67.4	32.2	<0.0001
Mental health									
Anxiety symptoms	32.8	30.3	0.49	24.7	29.1	0.04	17.7	21.1	0.006
Anxiety disorders	8.0	7.0	0.63	7.0	8.8	0.15	n/a	n/a	n/a
Depression[1]	31.1	23.9	0.04	22.7	25.9	0.0008	18.1	25.7	0.004
Any aggressive behaviour	43.9	48.3	0.23	27.1	33.6	0.003	9.9	7.9	0.03
Hallucinations/ Delusions	5.9	NR	0.44	7.2	7.6	0.75	4.3	3.3	0.12
Social isolation	4.9	9.1	0.09	6.3	13.4	<0.0001	15.4	19.3	0.0006
Psychotropic drug use									
Antipsychotics	30.9	42.7	0.0006	19.7	27.0	0.0002	10.7	20.0	<0.0001
Antidepressants	46.8	58.4	0.002	29.1	33.6	0.04	24.9	36.3	<0.0001
Anxiolytics	14.7	22.5	0.003	29.8	39.5	<0.0001	16.4	22.2	<0.0001
Sedatives	11.5	23.0	<0.0001	15.5	15.6	0.94	20.9	25.2	0.0008

Abbreviations: COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; HIV, human immunodeficiency virus; STI, sexually transmitted infection; UTI, urinary tract infection; NR, not reported (due to small cell size, <9 cases)
[1]Symptoms of probable depression defined as a score of ≥3 on the Depression Rating Scale

cohorts in all the settings had higher rates of tuberculosis infections. Rates of antibiotic-resistant infections, cellulitis and *C. difficile* were all higher in the HIV-positive cohort in the CCC and LTC settings. Septicemia prevalence was higher in the HIV-positive group in CCC, and STIs were much more prevalent in the HIV-positive cohorts in both LTC (6.7% vs. 0.1%) and CCC (12.1% vs. 0.1%).

Chronic disease diagnoses

Chronic disease prevalence was generally lower among PHAs, with the exception of chronic psychiatric conditions, which were more common among HIV-positive individuals in home care ($p < 0.0001$) (**Table 2**). In the LTC setting, heart failure was lower in the HIV-positive group, but the rates of COPD, diabetes and cancer were similar between the HIV-positive and negative groups. In CCC and home care, the HIV-positive group had rates of COPD similar to the HIV-negative group but lower rates of heart failure, diabetes and cancer. Other cardiovascular diseases were significantly lower in the HIV-positive group in all three settings ($p < 0.0001$).

Mental health issues

Mental health issues were generally common and similar among LTC residents with and without HIV (**Table 2**). In CCC and home care, PHA had slightly higher rates of anxiety symptoms but these were not statistically significant. While aggressive behaviour was more prevalent in the HIV-positive cohort in CCC (33.6% vs. 27.1%), it was less prevalent in the HIV-positive cohort in home care (7.9% vs. 9.9%). The HIV-positive group experienced significantly more social isolation than the HIV-negative group in the CCC and home care settings ($p < 0.0001$). Finally, across all care settings, rates of psychotropic drug use were higher in the HIV-positive versus the HIV-negative groups, but were not statistically significant for antidepressants and sedatives in the CCC setting.

Discussion

This is the largest study to date of PHAs living in care settings. It included 1,608 PHAs from across Canada and confirms work done in an earlier Ontario cohort study (26). Compared to their counterparts without HIV, older PHAs had more co-infections, fewer chronic diseases and a similar mental health profile, although they tended to use more psychotropic medications. With the exception of UTIs, co-infections were more common among PHAs in all care settings, consistent with previous research (27,28). The rates of comorbid diseases varied among PHAs, with lower overall prevalence than reported in earlier work (3-11). The younger age of PHA groups in this study may explain these findings, but we were not able to confirm this as the PHA sample size was not large enough to stratify by age.

This study also confirms the high prevalence of psychiatric diagnoses, depression and anxiety symptoms among older PHAs (2,7,8,11,29-31). However, the prevalences of anxiety disorders and hallucinations or delusions were also quite high among the HIV-negative cohorts in these care settings. The prevalence of depression neared 25% among PHAs, which is slightly higher than rates of 21% in US nursing homes (28,32).

The substantially higher rates of psychotropic medication use by HIV-positive groups appear to be a novel finding. Since this is a descriptive dataset, it is not possible to speculate on the appropriateness of this use. Rates of social isolation were higher among PHAs, especially in home care. Social isolation, known to be common among older PHAs, increases with age (3) and can lead to loneliness and depression (2).

Key strengths of this study are its inclusion of large samples from multiple sites and data from across Canada. These findings can be considered representative of the three care settings that were explored, as interRAI data are complete where mandated. Finally, these data allowed characterization of the specific needs of older PHAs as they begin to navigate care options in older age.

Nevertheless, the over-representation of data from Ontario and the variability of interRAI uptake across Canada are important limitations. Also, these findings cannot be compared to PHAs who do not access such care or who access AIDS/HIV-specific care from other care settings. Finally, this cross-sectional work could not determine causal relationships.

As the population ages, the demand for LTC to support, treat and care for older PHAs will increase. Failure to address the unique care needs of this group may lead to worse outcomes and increase the strain on health systems (33). The higher prevalence of psychotropic medication use among HIV-positive groups may be worthy of more attention, especially given the debate over the appropriateness of these therapies in general (34,35). Monitoring of these trends is indicated.

Future research using a comprehensive national sample of older PHAs would provide information to regions excluded in the current study. Exploring policy options designed to improve both care and access in these settings should also be a priority, particularly in the home care setting where improved services could delay or prevent hospitalizations and LTC admissions.

Conclusions

More PHAs are living longer and experiencing HIV in the context of aging. Our findings suggest that PHAs in home care, LTC and CCC settings have major needs with respect to the management of co-infections, comorbidity and mental health issues that set them apart from their HIV-negative counterparts.

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Conflict of interest

All authors confirm that they have no conflicts of interest.

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Hepatitis C in Canada and the importance of risk-based screening

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Abstract

Chronic hepatitis C (CHC) remains a public health issue affecting an estimated 220,000 individuals in Canada. In 2011, approximately 44% of those with CHC were unaware of their infection. Hepatitis C is infectious in origin, and if left untreated, can lead to significant morbidity and mortality in its chronic form, including liver cirrhosis, hepatocellular carcinoma and liver failure. These health outcomes are associated with comorbidities, adding a burden to the Canadian health care system. Recent advancements in the treatment of hepatitis C have changed the clinical landscape.

In Canada, the prevalence of incident cases is higher in specific population groups. Injection drug use (IDU) currently accounts for the highest proportion of new hepatitis C virus (HCV) infection. It is unclear to what extent HCV infection through health care or personal services use contributed to current prevalent cases of CHC. The Canadian Task Force on Preventive Health Care (CTFPHC) is currently reviewing the evidence for different approaches to HCV screening and the benefits and harms of screening. Risk-based screening remains critical to detecting hepatitis C as knowing one's status has been linked to the cascade of care and improved population health outcomes. This article intends to highlight risk factors associated with the acquisition of HCV so that health care providers can screen, where appropriate, and detect CHC.

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Introduction

Hepatitis C, an inflammation of the liver caused by the hepatitis C virus (HCV), is infectious in origin and can lead to chronic disease with the added dimension of transmission. Hepatitis C is often asymptomatic for decades until liver damage is already underway, highlighting the importance of early detection.

The primary route of transmission is through blood-to-blood contact with an infected individual or product. HCV can cause acute and chronic hepatitis C (CHC). Approximately 25% of individuals with acute hepatitis C will spontaneously clear the virus (1); the remaining 75% develop CHC, which may progress to cirrhosis, liver failure or hepatocellular carcinoma (2).

Of the seven HCV genotypes known worldwide (3), genotype 1 is the most common in Canada (4) and, until recently, has been difficult to treat. Approvals of new pharmaceuticals for the management of CHC in Canada have the potential to make CHC a curable infectious disease.

In Canada, 346 deaths were attributed to CHC in 2011 (5); however, the number of hepatitis C-related deaths is likely considerably underestimated due to misclassification on death certificates (6). Data from the Canadian Organ Replacement Registry indicate that 21% of patients who received liver transplants from 2004 to 2013 in Canada had a primary diagnosis of HCV (7). In a 2010 Ontario study, HCV was ranked as one of the most burdensome infectious pathogens in terms of years of life lost due to premature mortality, year-equivalents of reduced functioning, and health-adjusted life years (8), underscoring the impact of this infection on the health of Canadians.

In 2012 and 2013, the Centers for Disease Control and Prevention (CDC) and the U.S. Preventive Services Task Force (USPSTF) released updated guidelines on HCV screening, recommending that all adults born between 1945 and 1965 (also known as "baby boomers") should receive baseline screening for HCV regardless of their risk factors (9,10). The US recommendations to undertake one-time testing of baby boomers were based on epidemiological data demonstrating 1) a high prevalence of HCV in the baby boomer birth cohort; 2) a high proportion of patients with undiagnosed infection; 3) a projected increase in the burden of disease; and 4) indirect evidence linking screening with improved health outcomes (9,10).

Following the release of the US recommendations, the Public Health Agency of Canada examined the projected burden related to hepatitis C (11) and modelled prevalence estimates for anti-HCV and CHC (12). Given the uncertainty around the estimates and the benefits and harms of screening, further analysis was required to determine whether changes should be made to Canada's current risk-based screening

recommendations. These areas will be addressed by the Canadian Task Force on Preventive Health Care (CTFPHC). CTFPHC is conducting a review of Canadian data to determine the applicability of different screening approaches, including birth cohort screening, in Canada.

The objectives of this article are to highlight the risk factors that contribute to transmitting and acquiring HCV and to encourage health care providers to assess the need for HCV screening as part of routine medical care while we wait for the results of the assessment of the evidence for birth cohort screening in Canada.

Pharmaceutical management

The goal of hepatitis C therapy is to achieve a sustained virological response (SVR), defined as having an undetectable viral load in the blood following treatment. Until recently, treatment for hepatitis C consisted of injections of pegylated interferon-alfa and ribavirin, which resulted in <60% SVR (13). In addition, the therapies lasted a long time (up to 48 weeks), involved injections and had significant adverse effects (e.g. anemia, fever), which limited the efficacy and tolerability among patients (13,14).

In December 2014, Health Canada approved new short-course interferon-free treatments (15). Genotype 1 patients treated with these new regimens can achieve a SVR of >90%, with fewer side effects (14,16,17). These new treatments present an opportunity to reduce the morbidity and mortality associated with hepatitis C and the burden on the health care system. The introduction of the new therapies has shifted the focus from living well with hepatitis C to potentially curing hepatitis C.

Epidemiology

In Canada, HCV has been a notifiable infection under national surveillance since 1991. Provincial and territorial health authorities report cases of HCV infection to the Canadian Notifiable Disease Surveillance System (CNDSS). The latest surveillance data indicate that between 2005 and 2012 the rate of reported cases of HCV decreased steadily from 40.4 per 100,000 to 29.3 per 100,000 population. Rates declined among both males and females in all age groups, with the exception of small increases in males aged 60 years and older and females aged 25 to 29 years. Over the eight-year time frame, rates of reported cases of HCV were consistently higher in males than in females (18). Although information on acute or CHC status was not available from most provinces and territories, CHC infection probably makes up the majority of cases reported to the CNDSS, as acute infection is usually asymptomatic and less likely to be diagnosed (18).

An analysis of cohort effects among cases of HCV reported between 1991 and 2010 in Canada found that those born between 1946 and 1965 contributed more than half of all cases (19). While the rate of reported cases in Canada appears to be decreasing, the number of individuals infected decades ago and now developing sequelae is expected to increase as their disease progresses (20).

Population-based studies of the prevalence of HCV infection provide additional information on the extent of this disease. The Canadian Health Measures Survey (CHMS) found the seroprevalence of HCV antibody (anti-HCV), a marker of lifetime exposure to the virus, to be 0.5% of the household-dwelling population in Canada over a period of data collection spanning 2007 to 2011 (21). However, modelled prevalence estimates, taking into account vulnerable populations not surveyed by the CHMS, such as the homeless, prison inmates and foreign-born populations who do not speak English or French, indicate that the rate of anti-HCV in the Canadian population may be closer to 1% (plausibility range, 0.6%–1.3%) (12). The prevalence of CHC was estimated to be 0.6%, with approximately 44% of those being unaware of their infection (12).

Risk factors

Risk factor information available through national surveillance of HCV is limited; however, there is a considerable research on the conditions that influence the likelihood of becoming infected with the virus. An overview of practices that increase the risk of acquiring HCV, as well as populations that have been reported to have higher than average rates of HCV infection, is presented below.

Injection drug use

Injection drug use (IDU) continues to be the primary cause for incident cases of HCV in developed countries (19). In Canada, among newly acquired HCV cases with known risk factor information, 61% had reported a history of IDU (22). In addition, a 2010–2012 survey of people who injected drugs found that 68% of those surveyed had evidence of exposure to HCV in their lifetime (23). The high prevalence of HCV infection among injection drug users coupled with the high infectivity of HCV make preventing HCV transmission challenging (24,25). IDU or sharing needles or other drug use equipment (i.e. filters, syringes, pipes, spoons), even once, increases the risk of acquiring or transmitting hepatitis C.

Contaminated medical, dental or personal services equipment

Lack of implementation of standard infection prevention and control practices in health care (e.g. in hospitals, dental offices) or personal service (e.g. tattoo parlours and nail salons) is another risk for HCV infection (26-30). For instance, patients undergoing hemodialysis are at increased risk of acquiring HCV, especially if the equipment has been reused or improperly sterilized (26). In addition, a recent systematic review of international publications reported that health care workers in direct contact with patients or blood (from needle stick injuries) are 1.6 times more likely to be infected with HCV than the general population. Increased prevalence of HCV was found among medical staff (OR 2.2), laboratory staff (OR 2.2) and dental staff (OR 3.5) compared to controls (27). HCV outbreaks have also occurred in colonoscopy clinics in Canada (31-35).

Unsafe tattooing practices using non-sterile equipment increase the risk of acquiring HCV (28). Results from a systematic review

indicate that risk of HCV increases with increase in the surface area covered by tattoos as well as the number of tattoos (28).

The key to reducing the risk of transmitting infectious diseases in health care and personal service settings is to ensure appropriate education and, training of personnel to be compliant with infection prevention and control practices (29,30).

Blood, blood products and organ transplantation before 1992

Prior to implementing routine screening of donated blood, blood products and organs in 1992, transfusion and transplantation procedures represented a significant risk for HCV transmission. These risks have been minimized in Canada through routine screening and disposal of donations that contain a transmissible disease; however, this is not the case for all countries. Canadian Blood Services data from 2014 indicate that HCV was detected in 6.1 per 100,000 donations; the residual risk of becoming infected with HCV through receipt of a unit of blood is estimated to be very low at 1 in 6.7 million donations (36).

Vertical transmission

Mother-to-child or vertical transmission of HCV may occur when an infant is born to a woman with HCV infection. Results from a recent meta-analysis suggest that the risk of vertical transmission from anti-HCV positive and RNA-positive women is about 5.8% (95% CI, 4.2%–7.8%), and the risk to children born to an anti-HCV positive mother with spontaneous clearance of infection (RNA negative) was insignificant (37,38).

Other activities that may result in contact with contaminated blood

Sharing personal care items such as razors, toothbrushes or nail clippers with someone who is HCV-positive is a risk, of a less common one, for acquiring hepatitis C because HCV can remain infectious on inanimate surfaces for up to 6 weeks (24).

Though risk for sexual transmission of HCV during intercourse is low (39), engaging in risky sexual behaviour, such as anal sex without a condom, could result in HCV transmission (40-42) if the mucosa breaks, leading to blood-to-blood contact.

Populations with a higher prevalence of HCV infection

Men who have sex with men

Some studies have demonstrated higher rates of HCV infection among HIV-positive men who have sex with men (MSM) compared to HIV-negative MSM (43,44). Some HIV-positive MSM may be more likely to engage in practices that increase the risk of HCV transmission. These practices may include high-risk sexual behaviour (e.g. unprotected anal intercourse or fisting, which may lead to bleeding); IDU and the use of recreational drugs that have been linked to high risk sexual activity; and serosorting (i.e. choosing sexual partners with the same HIV status as one's own), which has also been linked to transmission of sexually transmitted and bloodborne infections among HIV-positive MSM. In addition, the HIV infection itself, as well as co-infection with other sexually transmitted infections (e.g. syphilis, gonorrhea or chlamydia), may increase susceptibility to HCV through ulceration of genital mucosa or suppression of the immune system (41-43,45-47).

Incarcerated populations

High rates of HCV infection have been found among inmates of federal and provincial penitentiaries through routinely offered screening. Although not all inmates accept HCV screening, those identified with CHC are offered treatment depending on their stage in liver fibrosis (48). Recent surveillance data from Correctional Services Canada indicate that 86.1% of federal penitentiary inmates accepted HCV screening on admission and 18.5% were positive for HCV in 2012 (49). Risk factors for HCV acquisition among inmates include contact with infected blood through fights, sexual exposure, IDU or unsafe tattooing practices (50 and *unpublished data Correctional Services Canada 2015*).

Aboriginal Peoples

Aboriginal Peoples appear to be disproportionately affected by HCV infection: a pilot survey of Aboriginal people in Regina, Saskatchewan, conducted from 2011-2012 found that 42% of participants had evidence of exposure to HCV in their lifetime (51-53). As with non-Aboriginal Canadians, IDU is the primary risk factor; additional social determinants that may make Aboriginal people vulnerable to HCV infection include poverty, inadequate housing and lack of access to health care services (51).

Immigrants from countries with high HCV prevalence

Certain countries have a higher-than-average prevalence of HCV (greater than 3%); people who were born or resided for a significant period of time in such regions may be at increased risk of HCV infection, particularly in those regions where infection prevention and control measures in health care or personal service settings are not routinely implemented (54). Regions where hepatitis C is more common include Central, East and South Asia; Australasia and Oceania; Eastern Europe; Sub-Saharan Africa; and North Africa/Middle East (4,55).

Screening

Screening is a viable public health intervention when the following criteria are met: the condition being screened for should be an important health problem; the natural history should be well understood; there should be a detectable early stage; a suitable test should be available for the early stages; treatment at an early stage should be more beneficial than at a later stage; the availability of a diagnostic test should be accepted; intervals for repeat testing should be determined; adequate health service provisions should be available; the benefits should outweigh the harms; effective treatment should be available and accessible; and lastly, the cost should be balanced against the benefits (56).

Screening for CHC may provide both public health and personal health benefits by interrupting viral transmission (public benefit) and reducing morbidity and mortality (personal benefit). Achieving SVR is associated with a reduced risk of hepatic events and with patients living healthier lives (57). In addition, early

diagnosis enables counselling to reduce alcohol consumption, which can slow the progression of liver disease (58).

The public health benefit of identifying undiagnosed cases through risk-based screening is to prevent the acquisition and transmission of HCV in incident cases. A case is being made for birth cohort screening identifying individuals with CHC who might otherwise remain undiagnosed. The CTFPHC's assessment will shed light on the applicability of birth cohort screening in Canada. Health care practitioners are encouraged to assess the need for HCV screening as part of routine care.

Risk-based screening for hepatitis C

Current screening recommendations for hepatitis C in Canada are based on the assessment of risk factors (59). Risks associated with the acquisition of HCV include activities that involve any risk of exposure to contaminated blood or products including:

- IDU or sharing contaminated drug equipment, even once
- Receipt of health care or personal services, where there is a lack of infection prevention and control practices
- Receipt of a blood transfusion, blood products or organ transplant before 1992 in Canada
- Birth or residence in a region where hepatitis C is more common (prevalence >3%), including Central, East and South Asia; Australasia and Oceania; Eastern Europe; Sub-Saharan Africa; and North Africa/Middle East
- Other Risks:
    - Sharing personal care items with someone who is HCV-positive
    - Participating in risky sexual activity
    - Being born to a mother who is HCV-positive

Conclusion

Hepatitis C is a complex disease in that it is infectious, can remain asymptomatic for decades, can present as a chronic illness and is associated with other chronic comorbidities. The presence of comorbidities may have implications for the diagnosis, management and treatment success of CHC. With the availability of new effective treatment for hepatitis C, screening for hepatitis C is important for early detection and to improve population health and patient outcomes. Familiarity with the risk factors for the acquisition of HCV and identifying individuals who are at risk are important to reduce the morbidity and mortality related to hepatitis C and prevent onwards transmission.

Conflict of interest

None.

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Primary care pearls to help eliminate tuberculosis in Canada

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Abstract

Although Canada has a low incidence of tuberculosis (TB), certain populations, including the foreign-born and Canadian-born Indigenous peoples, continue to be disproportionately represented among reported cases. The overall incidence rates of active TB in Canada have not significantly changed in the past decade and work still needs to be done to reach TB elimination goals set by the World Health Organization (WHO). In trying to achieve TB elimination in Canada, primary care clinicians, with the support of public health professionals and TB experts, can help by focusing on 1) targeted screening and treatment of latent TB infection (LTBI) and 2) timely diagnosis and referral of active TB disease. The following article focuses on some key primary care considerations to keep in mind in day-to-day patient care. To help conduct targeted screening and treatment for LTBI, several key populations, including immigrants from high TB burden countries, Indigenous peoples and several other at-risk groups, are outlined. Reactivation of LTBI plays a significant role in TB burden and is likely an area of major potential impact in achieving TB elimination. Advancement in LTBI treatment, including short course therapy, is also described. In addition, to help make a timely diagnosis of active TB, several key risk factors, including several co-morbidities which increase the risk of developing TB disease, can be considered. Being front-line in patient care, keeping in mind some of these key pearls may aid primary care providers to have potential impact on eliminating TB in Canada.

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Introduction

In May 2014, the World Health Assembly approved the World Health Organization's (WHO's) post-2015 global strategy to end tuberculosis (TB) by 2035. The ambitious targets included reducing the global incidence of TB to fewer than 100 cases per 1,000,000 population; this would require a 95% reduction in the number of deaths due to TB and a 90% reduction in the incidence of TB by 2035, as compared to 2015 (1). For low-incidence countries, such as Canada, which have already reached a TB incidence of less than 100 per 1,000,000 population, the global strategy has been adapted to provide a framework for TB elimination, defined as less than 1 TB case per 1,000,000 population by 2050 (1).

Despite being a low-incidence country, there is still work to be done in order to eliminate TB in Canada. Based on *The Global Plan to Stop TB 2006–2015* (WHO) (2), Canada's goal was to reach a target incidence of 3.6 per 100,000 population per year by 2015, a target that was reiterated in the 2014 *Tuberculosis Prevention and Control in Canada: A Federal Framework for Action* (3). Between 2003 and 2013, the reported overall incidence rate of TB disease in Canada ranged from 5.2 cases per 100,000 population to 4.7 cases per 100,000 population, respectively (4). Although the incidence of active TB disease in the overall Canadian population is among the lowest in the world, the rates have not significantly changed in the past decade. Foreign-born and Canadian-born Indigenous populations continue to be disproportionately represented among reported cases. In 2013, the foreign-born population, which represented approximately 22% of the total Canadian population, accounted for 71% of reported cases, whereas Canadian-born Indigenous people, who made up 4% of the total Canadian population, accounted for 19% of reported cases (4).

The WHO action framework cites several challenges to TB elimination in low-incidence countries, including diminishing clinical and diagnostic expertise, as well as diminishing awareness of TB as a result of the fall in incidence (1). One of the eight outlined priority action areas for these countries include undertaking screening for latent TB infection (LTBI) and active TB among contacts and selected high-risk groups, and providing appropriate treatment (1).

Primary care clinicians provide care for individuals from diverse backgrounds and will inadvertently be caring for populations who are at increased risk for both TB disease and TB infection. As TB incidence rates decline in Canada, the overall level of physician experience with the disease will also decline. Hence, as important as it is for experienced clinicians to manage TB cases, it is just as much a priority to keep referring physicians, including those in primary care, abreast of developments in TB screening and disease management (5).

Primary care clinicians, with the support of public health professionals and TB experts, have two key roles in Canada's elimination efforts: conducting targeted screening and treatment of LTBI, which prevents reactivation and helps accelerate the decline in TB incidence, and making timely diagnosis of active TB disease, which prevents further transmission and helps maintain the decline in TB incidence.

Targeted screening and treatment for latent TB infection

Based on recent data presented at the Advisory Council for the Elimination of Tuberculosis (ACET) at the Centers for Disease Control and Prevention in December 2015, the number of TB cases originating from reactivation of LTBI may be even higher than previously thought (6). Advisory Council members determined that targeting LTBI would be an area of biggest potential impact on achieving TB elimination goals; however, it is a daunting task.

Each year approximately 250,000 immigrants and refugees settle in Canada (7,8). As part of the Immigration Medical Examination (IME) conducted on individuals applying for permanent residency and some categories of temporary residency, those aged 11 years and older should have a chest x-ray completed in their country of origin (8,9). Based on the IME history and a physical examination, anyone suspected of having active TB should be referred for further assessment in their country of origin and those diagnosed with active TB must complete their treatment before arriving in Canada (7).

Post-immigration surveillance of selected immigrants considered high risk for developing active TB is also based on certain risk factors found in the IME (7).The goal of the IME is to ensure that migrants with active TB are diagnosed, treated and no longer infectious prior to arriving in Canada; it does not aim to detect or treat LTBI (8). Neither tuberculin skin tests (TST) nor interferon-gamma release assays (IGRA) are routinely done on newcomers to Canada. Mass screening of this entire population is not recommended since it would be logistically impossible and largely ineffective.

The selection of individuals for targeted LTBI screening and treatment is based on their risk of prior exposure to TB and their risk of reactivation, balanced against the likelihood of safe completion of treatment, including the risk of hepatotoxicity (10). Determining which patients may benefit from LTBI screening and treatment may not be straightforward in all circumstances. **Table 1** is based on the most recent *Canadian Tuberculosis Standards, 7th Edition*, developed by the Canadian Thoracic Society and the Public Health Agency of Canada. It summarizes seven select groups from various at-risk populations that primary care physicians may commonly encounter in their practice and who they should consider for targeted LTBI screening.

A free online tool is available from McGill University (http://www.tstin3d.com/) to help interpret TST or IGRA results by estimating the risk of developing active TB disease using the key risk factors discussed in **Table 1** (14). Nevertheless, clinicians must always balance the patient's risk of reactivation and the capacity for ongoing follow-up if screening and treatment are offered. The likelihood of safe completion of treatment, including ongoing monitoring for potential adverse effects, such as hepatotoxicity, while on treatment also needs to be considered (10). If screening is offered and the patient is suspected to have LTBI based on a positive TST or IGRA, active disease must be excluded carefully before initiation of LTBI therapy. Exclusion of active TB disease typically includes a symptom screen, chest x-ray and sputum smear and culture.

Advances in treatment for latent TB infection

Significant progress has been made in improving the lengthy LTBI therapy. A multicentered, multinational randomized control noninferiority trial with approximately 4,000 patients per arm demonstrated that rifapentine and isoniazid (commonly known as 3HP) administered once weekly for a total of 12 doses given directly observed was as effective as the current international standard of 9 months (252 doses) of daily isoniazid self-administered for the treatment of LTBI (15).The 3HP regimen also resulted in a higher completion rate. A more recent randomized control trial (RCT) in the pediatric population also evaluated the effectiveness of 3HP therapy. In this study, which included 905 patients between the ages of 2 and 17 years, 3HP was shown to be as effective as isoniazid alone in preventing TB disease in children and also had higher completion rates compared to the standard 9 months of isoniazid (16).

At present, 3HP treatment for LTBI is available in Canada through Health Canada's Special Access Programme only.

Making a timely diagnosis of active TB disease

Although the rate of TB transmission in the general population in Canada is low, active TB disease and transmission is seen in at-risk groups, including during outbreaks in Indigenous communities and in some aggregate settings (such as shelters, prisons, schools, etc.). Making a timely diagnosis is critical to interrupting transmission and is a main priority in TB control.

The patient's history, including key risk factors, signs and symptoms, and his/her chest x-ray is paramount to the diagnosis of TB disease. Among new Canadians, their countries of origin and the time since arriving in Canada are key. Recent evidence from a large retrospective epidemiological study in Ontario suggests that immigrants from 6 countries (Afghanistan, China, India, Pakistan, the Philippines and Vietnam) accounted for 87% of active TB cases detected through pre-immigration screening, while those from 10 high-incidence countries accounted for 80% of active TB cases detected through post-immigration surveillance (7). In addition, this study demonstrated that the category of immigrants was associated with an increased risk of developing active TB disease following their arrival in Canada, with live-in caregivers and refugees at the highest risk (7). The risk of active TB disease reactivation is highest in the first two years following arrival and decreases with every subsequent year (17). In addition, in the medical history it is important to elicit the region of residence and ethnicity of Canadian-born individuals since some regions and populations within Canada, including Canadian-born Indigenous peoples, have higher TB incidence. Other important risk factors are listed in **Table 2**.

Presence of one or more high or moderate risk factor in a patient with symptoms and an epidemiological risk for TB can greatly increase the probability of a TB diagnosis (18). Signs

Table 1: Recommendations of the Canadian Thoracic Society for groups for targeted latent TB infection screening

Group at risk	Group to be screened (age range/limit for screening)
1. Close contacts of an active case of pulmonary TB	As soon as possible after diagnosis of the index case (Any age)Contacts grouped as follows (11): • High priority: household contacts plus close non-household contacts who are immunologically vulnerable, e.g. children <5 years • Medium priority: close non-household contacts with daily or almost daily exposure, including those at school and work • Low priority: casual contacts with lower amounts of exposure Index case as follows (11): • Smear-positive cavitary/laryngeal TB: initial contact follow-up includes both high- and medium-priority contacts • Smear-negative, non-cavitary pulmonary TB: initial contact follow-up of high-priority contacts only
2. Immigrants from countries with high TB incidence[1] (defined as ≥30 cases/100,000 population for all forms of active TB cases)	Fibronodular changes on chest x-ray (usually in the context of post-landing surveillance) [Any age] All children and adolescents as soon as possible after arrival (Up to age 20 years) Refugees (20–50 years) Immigrants and refugees with underlying medical comorbidities with the following risk of TB reactivation[2]: • High risk (Any age) • Moderate risk (Up to 65 years) • Slightly increased risk (Up to 50 years)
3. Indigenous peoples[3]	Varies by TB risk in the community (12) Follow up of close contacts of an active case of pulmonary TB (as above) [Any age] In the presence of underlying medical comorbidities with the following risk of TB reactivation[2]: • High risk (Any age) • Moderate risk (Up to 65 years) • Slightly increased risk (Up to 50 years)
4. Injection drug user OR the homeless	In the presence of underlying medical comorbidities with the following risk of TB reactivation[2]: • High risk[4] (Any age) • Moderate risk (Up to 65 years) • Slightly increased risk (Up to 50 years)
5. Medical comorbidities (including HIV)	All individuals, regardless of prior TB exposure, should be considered for screening if they have certain medical comorbidities that increase risk of TB reactivation[2]: • High risk (Any age) • Moderate risk (Up to 65 years) • Slightly increased risk (Up to 50 years)
6. Travellers to countries with high TB incidence[5]	≥1 month of travel with very high-risk contact, particularly direct patient contact in a hospital or indoor setting, but possibly including work in prisons, homeless shelters, refugee camps or inner city slums (Up to 50 years if single post-travel TST) ≥3 months of travel to TB incidence country >400/100,000 population[1] (Any age if documented TST conversion) ≥6 months of travel to TB incidence country 200–399/100,0001 population[1] (Any age if documented TST conversion) ≥12 months of travel to TB incidence country 100–199/100,000 population[1] (Any age if documented TST conversion)
7. Residents of long-term care facilities	Baseline posterior–anterior and lateral chest x-ray on admission for those from at-risk population6 (>65 years) [13] Baseline two-step TST upon admission for at-risk population[6] (≤65 years) [13] Annual TST not necessary (13) TST no longer recommended as a primary assessment tool in the contact follow-up of elderly residents in long-term care; focus should be on early detection of secondary active cases (13)

Source: Can Respir J. 2013;20(SA):119A-128A.(8)
Abbreviations: HIV, human immunodeficiency virus; TB, tuberculosis; TST, tuberculin skin test
[1]See http://data.worldbank.org/indicator/SH.TBS.INCD for the most recent TB rates by country.
[2]Risk of reactivation for different medical comorbidities (by risk category) outlined in Table 2 below
[3]The TB Standards provide multifactorial considerations when considering TB in this population
[4]For those at high risk, strongly consider measures to enhance adherence, such as directly observed LTBI treatment and/or use of incentives and enablers. For all others, only consider LTBI screening and treatment provided treatment completion and adequate follow-up for hepatotoxicity can be achieved
[5]For those >50 years and at higher risk of prior TB exposure, i.e. foreign-born, current or previous injection drug user, Indigenous people, health care workers or those with pre-existing liver disease (i.e. people in whom the distinction between conversion and long-standing infection is particularly important), consider doing a pre- and post-travel TST to detect recent conversion. In this case, performance of two-step TST pre-travel would enhance the accuracy of testing after travel to detect true conversions from recent infection. For all other travellers, perform a single TST 2 months after return from travel. For individuals who are expected to undergo serial or repeated testing (e.g. health care workers), a pre-travel two-step TST is recommended (IGRA is NOT recommended).
[6]At-risk populations: history of active TB; staff and residents of homeless shelters; urban poor; staff and inmates of correctional facilities and previously incarcerated people; injection drug users; Indigenous people residing in communities with high TB rates; people infected with HIV; people born in Canada and other low-incidence countries prior to 1966; people born or previously residing in high-incidence countries; people with high medical risk factors listed in Table 2; health care workers serving at-risk groups (11).
Note: For Groups 1, 2 & 5, conditional recommendation, based on moderate to weak evidence. For Groups 4 & 6, conditional recommendation, based on weak evidence.

and symptoms of TB disease include weight loss, fevers, chronic cough, night sweats and hemoptysis. Although many of these symptoms are common to other diseases that present in low-incidence countries, they should be used in the context of a history that increases the pre-test probability of TB disease. In a recent review, several important clinical pearls are presented addressing seven clinical questions, six related to patient history and one related to laboratory/radiographic workup to help make

Table 2: Risk factors for the development of active tuberculosis among individuals presumed to be infected with Mycobacterium tuberculosis

Level of risk	Risk factor	Estimated risk for TB[1]
HIGH	AIDS	110–170
	HIV	50–110
	Transplantation (related to immunosuppressive therapy)	20–74
	Silicosis	30
	Chronic renal failure requiring hemodialysis	7–50
	Carcinoma of head and neck	11.6
	Recent TB infection (≤2 years)	15.0
	Abnormal chest x-ray – fibronodular disease	6–19
MODERATE	Tumour necrosis factor (TNF) alpha inhibitors	1.5–5.8
	Diabetes mellitus (all types)	2–3.6
	Treatment with glucocorticoids (≥15 mg/day prednisone)	4.9
	Young age when infected (0–4 years)	2.2–5
SLIGHTLY INCREASED	Heavy alcohol consumption (≥3 drinks/day)	3–4
	Underweight (<90% ideal body weight; for most people, this is a body mass index ≤20 kg/m2)	2–3
	Cigarette smoker (1 pack/day)	1.8–3.5
	Abnormal chest x-ray – granuloma	2

Adapted from Can Respir J. 2013; 20(Suppl A):45A (10)
Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus
[1]Relative to people with no known risk factor

a timely diagnosis of pulmonary TB (18).

The chest x-ray, including the classic adult presentation of upper lobe disease with fibronodular disease, cavities or pleural effusions, is often quite helpful in the diagnosis. However, it is important to note that active TB disease can still be present even if the chest x-ray is normal. It is paramount that all people who are suspected of having active TB disease have sputa sent for smear and culture to confirm the diagnosis and obtain susceptibilities. If a diagnosis of active TB is made, primary care practitioners should notify and collaborate with local public health services. Local public health professionals play a vital role in providing support in TB case management, including conducting contact investigations, providing TB medications and directly observed therapy for active cases. In addition, primary care providers should consider referring patients, especially complicated cases, to TB clinicians or specialized clinics for consultation and support with ongoing management.

Conclusion

Although Canada is a low-incidence country, the incidence rates of active TB disease in the overall population have not significantly changed in the past decade and striking disparity still exists in certain at-risk populations. When striving for TB elimination, primary care clinicians can be a part of the solution by focusing on 1) targeted screening and treatment of LTBI, and 2) timely identification and referral of active TB disease. Primary care providers, with their wide range of practices, inadvertently care for those populations who are at increased risk for both TB disease and TB infection and so play a vital role in the nation's overall TB elimination goals. Hence, they must remain up-to-date on TB prevention and control approaches and should consider the clinical pearls and resources described in this article in their day-to-day practice when caring for at-risk patients.

Conflict of interest

None.

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CASE REPORT

Zika virus, an emerging flavivirus, as a cause of fever and rash in a traveller returning from Central America

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Abstract

Fever in a returning traveller is a common clinical scenario for physicians in primary and acute care. Differential diagnoses for these patients are generated based on presenting clinical symptoms, travel destinations, potential exposure activities as well as the incubation period of common etiologic agents. In a case of fever and rash in a woman returning to Canada from El Salvador in November 2015, measles, dengue and chikungunya viral infections were queried as possible causes. Subsequent molecular testing using amplification of conserved regions of the flavivirus genome from nasopharyngeal and urine samples was positive, suggesting an active flavivirus infection. Sequencing was significant for the identification of Zika virus, a flavivirus that has only recently become endemic to Brazil and is now emerging throughout Central America. Zika virus should now be included in the differential diagnosis for travellers returning from Central and South America with a febrile illness and rash. To our knowledge this is the first reported case of Zika virus in Canada related to the most recent outbreak in Central America, South America and the Caribbean.

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Introduction

Zika virus is an emerging arthropod-borne member of the flavivirus genus that is closely related to other medically significant viruses including dengue, Japanese encephalitis virus, West Nile virus and yellow fever virus (1). Initially isolated from the Zika Forest in Uganda in 1947 (2), epidemiological surveys have shown evidence of serologic exposure in African countries including Gabon, Nigeria, Central African Republic and Sierra Leone (3-6) as well as in Southeast Asia, notably Indonesia, Malaysia and Thailand (7-10). Mosquitoes from the Aedes genus have been implicated as the primary vector of transmission of Zika virus (11). Recent outbreaks have occurred in several island nations in the South Pacific Ocean including Micronesia in 2007 (12), as well as French Polynesia, New Caledonia and the Cook Islands in 2013 and 2014 (13). Cases of Zika virus infection were first identified in the Americas in Brazil in 2014, and autochthonous transmission has been seen in northeastern regions of that country (14-15). As of December 2015, cases have been reported in other countries of Latin America including Venezuela, Suriname, Paraguay, Panama, Guatemala, Mexico, Colombia and El Salvador (16).

Case

A 52-year-old woman whose past medical history was significant for Parkinson's disease presented to the emergency department with fever and a new rash after recent travel to El Salvador.

The patient immigrated to Canada in 1992 from El Salvador. The primary purpose of her recent 14-day trip was to visit friends and relatives. She did not seek pre-travel medical advice, and her vaccination status was unclear. She stayed exclusively in San Salvador, the capital city of El Salvador. She denied any animal or fresh water exposures or any new sexual contacts. She received multiple mosquito bites during her visit. She felt well throughout her trip but noted subjective fevers along with myalgias and fatigue beginning five days after her return to Canada. She also had symptoms of conjunctivitis, but this was diminishing by presentation to the emergency room. An erythematous rash had initially developed on her face and spread to her trunk and arms the following day, which prompted the patient's presentation on day five of her illness.

On arrival, the patient was afebrile and non-toxic in appearance. Review of systems was significant for mild headache with no retro-orbital discomfort. She endorsed generalized myalgias and fatigue but no specific arthralgias. The patient denied significant respiratory or gastrointestinal symptoms. Examination was significant for a blanchable, maculopapular rash over the face that extended to the trunk, arms and upper legs. There was minimal conjunctival injection and no Koplik spots were identified. Cardiovascular and respiratory examinations were unremarkable and examination of the abdomen did not demonstrate splenomegaly.

Basic investigations collected on day five of the patient's illness were sent, including a complete blood count, which revealed mild leukopenia (3.2 x 109 cells/L;

reference: 3.5–10.5 x 109 cells/L) and mild thrombocytopenia (112 x 109 cells/L; reference 150–450 x 109 cells/L). Electrolytes, liver profile and renal function tests were normal. A chest x-ray was normal. Thin and thick malaria smears along with a *P. falciparum* rapid antigen test were negative. Rubella serology showed evidence of past infection/immunity. A monospot test was negative. HIV serology and syphilis enzyme immunoassay (EIA) were negative. Parvovirus IgM and IgG were negative. Blood cultures were negative, as was a throat culture. A throat swab for enterovirus polymerase chain reaction (PCR) was performed, and was negative. Hepatitis A serology showed evidence of immunity through previous infection or immunization. The patient was immune through vaccination for hepatitis B.

Despite her age, the history of a centripetal rash raised the possibility of measles, but both a nasopharyngeal swab (NPS) and a urine sample collected for measles PCR were negative. In addition, measles IgG showed evidence of prior infection/immunity. Dengue serology was ordered, and our patient was IgG positive and IgM negative, which is compatible with a history of previous flavivirus infection. PCR testing was then performed on the urine and NPS using a pan-flavivirus PCR targeting the NS5 gene (methodology previously described (17)). Both the urine and NPS were positive, but the signal strength was 10 times stronger in the NPS sample. The 217 base pair amplicon was sequenced, with a 216/217 base pair (99%) match for Zika virus (GenBank accession no. KF993678.1).

This diagnosis of Zika virus infection was available one week after the initial infectious diseases consultation. Repeat dengue serology, two weeks after first presentation, was positive for both IgM and IgG.

Discussion

This is the first reported case of Zika virus in Canada related to the most recent outbreak in Central America, South America and the Caribbean. Within a decade of the outbreak in Micronesia in 2007, Zika virus has been documented in several island nations in the South Pacific and, recently, in multiple countries in South and Central America. Zika virus is capable of transmission through numerous species of the Aedes genus, notably *Aedes aegypti* and *Aedes albopictus* (11). These species, which have adapted to urban and peri-urban environments, have been implicated in the rapid spread of chikungunya virus and dengue (18). Given the similarities in transmission vectors, it has been speculated that Zika virus has the potential to follow the epidemiological trends of these viruses and continue to gain footholds in Central America, the Caribbean and possibly more northern locales including parts of the southern United States (19). With ongoing transmission in Brazil and anticipated travel to the 2016 Rio de Janeiro Olympic Games, the potential for increasing incidence of imported cases in returning travellers is significant.

Clinical manifestations of Zika virus have been well characterized in previous outbreaks. The most common symptom described has been a macular or papular rash followed by subjective or measured fever (12). Of note, none of the temperatures of patients with confirmed Zika virus infection exceeded 37.9 °C in one prior outbreak (12). Other frequently described symptoms include arthralgias, conjunctivitis, myalgias, retro-orbital pain, and edema of the extremities (12-13). Symptoms typically last 3 to 12 days and overall disease course is thought to be milder than dengue or chikungunya (13); however, severe neurological complications including Guillain-Barre Syndrome have been described (12). In addition, the current epidemic in Brazil has now been linked to an increased incidence of congenital microcephaly (20), although further study is needed to confirm this association.

Given the non-specific clinical presentation of Zika virus infection, differentiating between Zika virus, dengue and chikungunya virus is difficult. Fever, rash, myalgias, arthralgias and retro-orbital pain are common symptoms of all three viruses. It has been suggested that extremity edema as well as conjunctivitis are more common in Zika virus (13) whereas severe arthralgias and persistent joint symptoms are more commonly associated with chikungunya (18). Cytopenias and lymphadenopathy are thought to be more common in dengue and chikungunya than in Zika virus infections (13). As well, the presence of a high fever may argue against Zika virus. Overt hemorrhagic fever has not been reported in association with Zika virus infection. Co-infection of Zika and dengue or other arboviruses is a concern given the common vector and geographic distribution. Differences in symptomatic presentation and disease severity due to co-infection are not known. In this case, the patient's primary symptoms of rash and fever abated one to two weeks after the initial onset of symptoms. The patient has noted ongoing mild generalized myalgias persisting past resolution of her other symptoms.

Supportive care with analgesics and antipyretics until symptom resolution is the mainstay of Zika virus infection management. Currently no directed treatment or vaccine is available. Zika virus infection is best prevented by avoiding mosquito vectors; travellers to endemic areas should wear long-sleeved clothing, use insect repellent and stay and sleep in screened-in or air-conditioned rooms.

Diagnosis of Zika virus is challenging as standard serologic testing cross-reacts significantly with other flaviviruses (12). In particular, dengue virus may present with a similar clinical syndrome and complicate serologic interpretation. A previous case in Canada described Zika virus in a traveller returning from Thailand, where a positive IgM for dengue initially led to a false diagnosis; this was corrected when the dengue IgG was persistently negative, leading the clinical team to investigate for other flaviviruses using molecular methods (21). In our patient, an initial negative IgM and a positive IgG for dengue likely reflects a history of dengue virus infection, with testing performed too early in the disease course to detect the cross-reacting IgM. Zika virus IgM typically develops within the first week of illness, and as our patient had only been ill for five days, the IgM response may not have developed at the time of testing (22). Repeat dengue IgM completed 19 days after illness onset was positive, showing the presence of acute cross-reacting Zika virus antibodies. A secondary flavivirus infection, as we were suspecting in our case, has been shown to induce a neutralizing antibody response with a greater degree of serologic cross-reactivity against other flaviviruses, which could further complicate interpretation of serologic testing (22).

For travellers returning from areas endemic for both Zika and dengue virus, molecular methods are likely to be more helpful

than serologic methods due to greater specificity and decreased turnaround time. The specimen recommended for Zika virus PCR is serum, during the first week after the onset of symptoms (23). Urine may be PCR positive for 10 days or longer after onset of symptoms (24). Testing from a NPS has been described, but it is unclear how long the virus will persist at this site (25). In our case, Zika virus was detected by the BCCDC Public Health Laboratory's PCR assay followed by amplicon sequencing. The sample was also sent to the National Microbiology Laboratory for confirmation. The NPS had a cycle threshold value of 27.46, a signal 10 times stronger than the urine, which had a cycle threshold value of 32.16. The results from molecular testing were also rapidly available, with the diagnosis of Zika virus made seven days after the initial assessment and specimen collection.

Conclusions

Zika virus is an emerging flavivirus that has become endemic in the Americas, having been recently documented in multiple countries across Central and South America. It should now be considered in all cases of returning travellers with fever and rash from these areas. Clinical presentation of Zika viral infection is similar to other medically important arboviruses including dengue and chikungunya virus. Measles can also have a similar presentation, posing additional challenges due to infection control implications. Serologic diagnosis is challenging given the cross-reaction with other flaviviruses, as well as the significant time delay in obtaining results. Prompt diagnosis is needed, as the differential diagnosis of fever and rash is broad in a returning traveller, and this would help to avoid unnecessary treatment or investigations. Molecular testing, with PCR and sequencing of the NS5 flavivirus gene, shows promise as a rapid and accurate diagnostic test for Zika virus, as well as for other flaviviruses. Given the possible association between Zika virus and microcephaly, pregnant women and women who could become pregnant should be counselled about this risk prior to travel to areas with documented Zika virus transmission. All travellers to these areas should be counselled on strategies to reduce exposure to mosquito vectors.

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Conflict of interest

None.

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Zika Virus Associated with Microcephaly

Source: Mlakar J, Korva M, Tul N, Popovi M, Poljšak-Prijatelj M, Mraz J et al. Zika Virus Associated with Microcephaly. New Engl J Med 2016 February 10, 2016DOI: 10.1056/NEJMoa1600651. http://www.nejm.org/doi/full/10.1056/NEJMoa1600651?query=featured_home.

In this report, we describe the case of an expectant mother who had a febrile illness with rash at the end of the first trimester of pregnancy while she was living in Brazil. Ultrasonography performed at 29 weeks of gestation revealed microcephaly with calcifications in the fetal brain and placenta. After the mother requested termination of the pregnancy, a fetal autopsy was performed. Microcephaly (an abnormally small brain) was observed, with almost complete agyria, hydrocephalus, and multifocal dystrophic calcifications in the cortex and subcortical white matter, with associated cortical displacement and mild focal inflammation. ZIKV was found in the fetal brain tissue on reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay, with consistent findings on electron microscopy. The complete genome of ZIKV was recovered from the fetal brain. This case shows severe fetal brain injury associated with ZIKV infection with vertical transmission... The complete genome sequence of ZIKV that was recovered in this study is consistent with the observation that the present strain in Brazil has emerged from the Asian lineage.

Extrahepatic manifestations of chronic hepatitis C virus infection

Source: Extrahepatic manifestations of chronic hepatitis C virus infection. Cacoub P, Comarmond C, Domont F, Savey L, Desbois AC, Saadoun D. Extrahepatic manifestations of chronic hepatitis C virus infection. Ther Adv Infect Dis. 2016 Feb;3(1):3-14. doi: 10.1177/2049936115585942. http://www.ncbi.nlm.nih.gov/pubmed/26862398.

During hepatitis C virus (HCV) chronic infection, extrahepatic manifestations are frequent and polymorphous. This article reports on a large cohort of patients with HCV-related autoimmune or lymphoproliferative disorders, from mixed cryoglobulinemia vasculitis to frank lymphomas. The relationship between HCV infection and such immune-related diseases has been formally demonstrated by epidemiological, clinical, immunological and pathological data, and results of therapeutic trials. More recently, other nonliver-related HCV disorders have been reported, including cardiovascular (i.e. stroke, ischemic heart disease), renal, metabolic and central nervous system diseases. For these manifestations, most evidence comes from large epidemiological studies; there is a need for mechanistic studies and therapeutic trials for confirmation. Beyond the risk of developing liver complications, that is, cirrhosis and liver cancer, patients with HCV infection have an increased risk of morbidity and mortality related to nonliver diseases. HCV chronic infection should be analyzed as a systemic disease in which extrahepatic consequences increase the weight of its pathological burden. The need for effective viral eradication measures is underlined.

Useful link

Committee to Advise on Tropical Medicine and Travel (CATMAT). Canadian Recommendations on the Prevention and Treatment of Zika Virus. http://www.healthycanadians.gc.ca/publications/diseases-conditions-maladies-affections/committee-statement-treatment-prevention-zika-declaration-comite-traitement-prevention/index-eng.php.

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